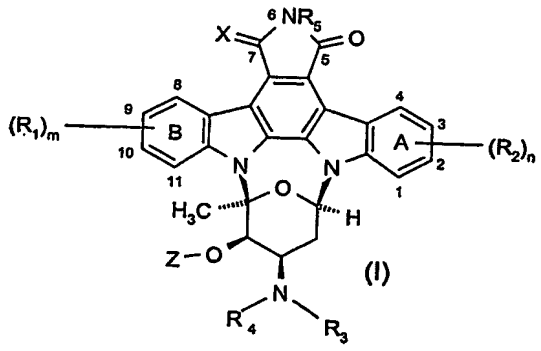
Staurosporine derivatives for hypereosinophilic Syndrome

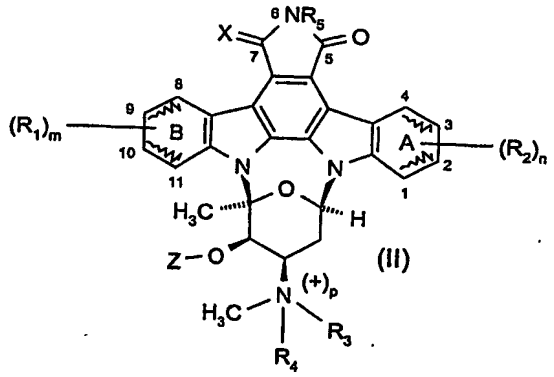
The present invention relates to the use of staurosporine derivatives (hereinafter: "STAUROSPORINE DERIVATIVES") for the preparation of a drug for the treatment of FIP1L1-PDGFRα-induced myeloproliferative diseases, especially for the curative and/or prophylactic treatment of hypereosinophilic syndrome and hypereosinophilic syndrome with resistance to imatinib, and to a method of treating hypereosinophilic syndrome and hypereosinophilic syndrome with resistance to imatinib, or other diseases associated with FIPL1-PDGFRa or similar mutations that activate PDGFRα.

The invention relates in particular to the use of staurosporines derivatives of formula



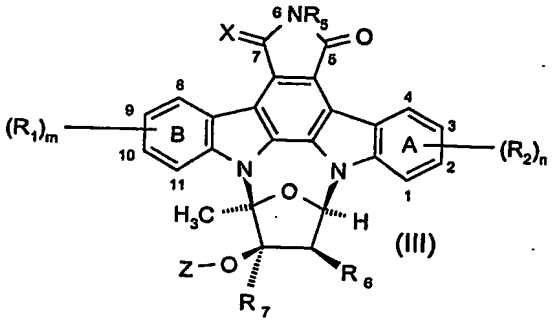
(I)

or



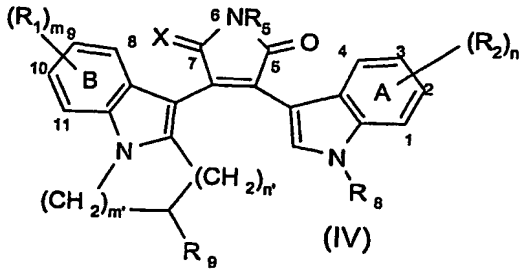
(II)

wherein (II) is the partially hydrogenated derivative of compound (I),



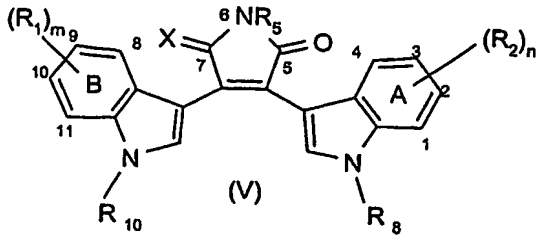
(III)

or



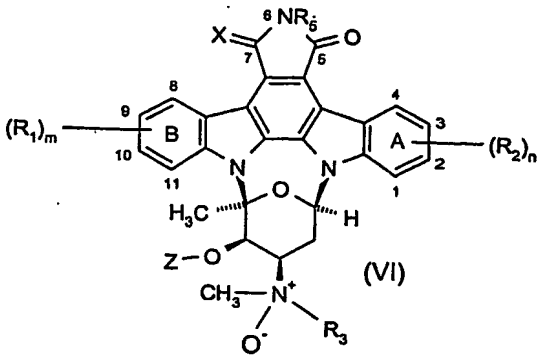
(IV)

or



(V)

or



(VI)

or

wherein R_1 and R_2, are, independently of one another, unsubstituted or substituted alkyl, hydrogen, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

n and m are, independently of one another, a number from and including 0 to and including 4;

n' and m' are, independently of one another, a number from and including 0 to and including 4;

R_3, R_4, R_8 and R_{10} are, independently of one another, hydrogen, $-O^{\cdot}$, acyl with up to 30 carbon atoms, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, an acyl with up to 30 carbon atoms, wherein R_4 may also be absent;

or if R_3 is acyl with up to 30 carbon atoms, R_4 is not an acyl;

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;

R_5 is hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, or a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon

atoms in each case, and in each case up to 9 heteroatoms, or acyl with up to 30 carbon atoms;

R_7, R_6 and R_9 are acyl or –(lower alkyl) –acyl, unsubstituted or substituted alkyl, hydrogen, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy,carbonyl, carbonyldioxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

X stands for 2 hydrogen atoms; for 1 hydrogen atom and hydroxy; for O; or for hydrogen and lower alkoxy;

Z stands for hydrogen or lower alkyl;

and either the two bonds characterised by wavy lines are absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present for the preparation of a pharmaceutical composition for the treatment of FIP1L1-PDGFRα-induced myeloproliferative diseases.

The general terms and definitions used hereinbefore and hereinafter preferably have the following meanings:

The prefix "lower" indicates that the associated radical preferably has up to and including a maximum of 7 carbon atoms, especially up to and including a maximum of 4 carbon atoms.

Lower alkyl is especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or tert-butyl, and also pentyl, hexyl, or heptyl.

Unsubstituted or substituted alkyl is preferably C_1-C_{20}alkyl, especially lower alkyl, typically methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or tert-butyl, which is unsubstituted or substituted especially by halogen, such as fluorine, chlorine, bromine, or iodine, C_6-C_{14}aryl, such as phenyl or naphthyl, hydroxy, etherified hydroxy, such as lower alkoxy, phenyl-lower alkoxy or phenyloxy, esterified hydroxy, such as lower alkanoyloxy or benzoyloxy, amino, mono- or disubstituted amino, such as lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, substituted mercapto, such as lower alkylthio, carboxy, esterified carboxy, such as lower alkoxycarbonyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, such as N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, sulfo, substituted sulfo, such as lower alkanesulfonyl or lower alkoxysulfonyl, aminosulfonyl or N-mono- or N,N-disubstituted aminosulfonyl, such as N-lower alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl.

Halogen is preferably fluorine, chlorine, bromine, or iodine, especially fluorine or chlorine.

Etherified hydroxy is especially lower alkoxy, C_6-C_{14}aryloxy, such as phenyloxy, or C_6-C_{14}aryl-lower alkoxy, such as benzyloxy.

Esterified hydroxy is preferably lower alkanoyloxy or C_6-C_{14}arylcarbonyloxy, such as benzoyloxy.

Mono- or disubstituted amino is especially amino monosubstituted or disubstituted by lower alkyl, C_6-C_{14}aryl, C_6-C_{14}aryl-lower alkyl, lower alkanoyl, or C_6-C_{12}arylcarbonyl.

Substituted mercapto is especially lower alkylthio, C_6-C_{14}arylthio, C_6-C_{14}aryl-lower alkylthio, lower alkanoylthio, or C_6-C_{14}aryl-lower alkanoylthio.

Esterified carboxy is especially lower alkoxycarbonyl, C_6-C_{14}aryl-lower alkoxycarbonyl or C_6-C_{14}aryloxycarbonyl.

N-Mono- or N,N-disubstituted carbamoyl is especially carbamoyl N-monosubstituted or N,N-disubstituted by lower alkyl, C_6-C_{14}aryl or C_6-C_{14}aryl-lower alkyl.

Substituted sulfonyl is especially C_6-C_{14}arylsulfonyl, such as toluenesulfonyl, C_6-C_{14}aryl-lower alkanesulfonyl or lower alkanesulfonyl.

N-Mono- or N,N-disubstituted aminosulfonyl is especially aminosulfonyl N-monosubstituted or N,N-disubstituted by lower alkyl, C_6-C_{14}aryl or C_6-C_{14}aryl-lower alkyl.

C_6-C_{14}Aryl is an aryl radical with 6 to 14 carbon atoms in the ring system, such as phenyl, naphthyl, fluorenyl, or indenyl, which is unsubstituted or is substituted especially by halogen, such as fluorine, chlorine, bromine, or iodine, phenyl or naphthyl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower alkylaminosulfonyl, or N,N-di-lower alkylamino-sulfonyl.

The indices n and m are in each case preferably 1, 2 or especially 0. In general, compounds of formula I in which n and m are in each case 0 (zero) are especially preferred.

An aliphatic carbohydrate radical R_3, R_4, R_8 or R_{10} with up to 29 carbon atoms, which is substituted by acyclic substituents and preferably has a maximum of 18, especially a maximum of 12, and as a rule not more than 7 carbon atoms, may be saturated or unsaturated and is especially an unsubstituted or a straight-chain or branched lower alkyl, lower alkenyl, lower alkadienyl, or lower alkinyl radical substituted by acyclic substituents. Lower alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, and also n-pentyl, isopentyl, n-hexyl, isohexyl and n-heptyl; lower alkenyl is, for example, allyl, propenyl, isopropenyl, 2- or 3-methallyl and 2- or 3-butenyl; lower alkadienyl is, for example, 1-penta-2,4-dienyl; lower alkinyl is, for example, propargyl or 2-butinyl. In corresponding unsaturated radicals, the double bond is especially located in a position higher than the α-position in relation to the free valency. Substituents are especially the acyl

radicals defined hereinbelow as substituents of R°, preferably free or esterified carboxy, such as carboxy or lower alkoxycarbonyl, cyano or di-lower alkylamino.

A carbocyclic or carbocyclic-aliphatic radical R_3, R_4, R_8 or R_{10} with up to 29 carbon atoms in each case is especially an aromatic, a cycloaliphatic, a cycloaliphatic-aliphatic, or an aromatic-aliphatic radical which is either present in unsubstituted form or substituted by radicals referred to hereinbelow as substituents of R°. An aromatic radical (aryl radical) R_3 or R_4 is most especially a phenyl, also a naphthyl, such as 1- or 2-naphthyl, a biphenylyl, such as especially 4-biphenylyl, and also an anthryl, fluorenyl and azulenyl, as well as their aromatic analogues with one or more saturated rings, which is either present in unsubstituted form or substituted by radicals referred to hereinbelow as substituents of R°. Preferred aromatic-aliphatic radicals are aryl-lower alkyl- and aryl-lower alkenyl radicals, e.g. phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, such as for example benzyl, phenethyl, 1-, 2-, or 3-phenylpropyl, diphenylmethyl (benzhydryl), trityl, and cinnamyl, and also 1- or 2-naphthylmethyl. Of aryl radicals carrying acyclic radicals, such as lower alkyl, special mention is made of o-, m- and p-tolyl and xylyl radicals with variously situated methyl radicals.

A cycloaliphatic radical R_3, R_4, R_8 or R_{10} with up to 29 carbon atoms is especially a substituted or preferably unsubstituted mono-, bi-, or polycyclic cycloalkyl-, cycloalkenyl-, or cycloalkadienyl radical. Preference is for radicals with a maximum of 14, especially 12, ring-carbon atoms and 3- to 8-, preferably 5- to 7-, and most especially 6-member rings which can also carry one or more, for example two, aliphatic hydrocarbon radicals, for example those named above, especially the lower alkyl radicals, or other cycloaliphatic radicals as substituents. Preferred substituents are the acyclic substituents named hereinbelow for R°.

A cycloaliphatic-aliphatic radical R_3, R_4, R_8 or R_{10} with up to 29 carbon atoms is a radical in which an acyclic radical, especially one with a maximum of 7, preferably a maximum of 4 carbon atoms, such as especially methyl, ethyl, and vinyl, carries one or more cycloaliphatic radicals as defined hereinabove. Special mention is made of cycloalkyl-lower alkyl radicals, as well as their analogues which are unsaturated in the ring and/or in the chain, but are non-aromatic, and which carry the ring at the terminal carbon atom of the chain. Preferred substituents are the acyclic substituents named herein below for R°.

Heterocyclic radicals R_3, R_4, R_8 or R_{10} with up to 20 carbon atoms each and up to 9 heteroatoms each are especially monocyclic, but also bi- or polycyclic, aza-, thia-, oxa-, thiaza-, oxaza-, diaza-, triaza-, or tetrazacyclic radicals of an aromatic character, as well as corresponding heterocyclic radicals of this type which are partly or most especially wholly saturated, these radicals – if need be – possibly carrying further acyclic, carbocyclic, or heterocyclic radicals and/or possibly mono-, di-, or polysubstituted by functional groups, preferably those named hereinabove as substituents of aliphatic hydrocarbon radicals. Most especially they are unsubstituted or substituted monocyclic radicals with a nitrogen, oxygen, or sulfur atom, such as 2-aziridinyl, and especially aromatic radicals of this type, such as pyrryl, for example 2-pyrryl or 3-pyrryl, pyridyl, for example 2-, 3-, or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl; analogous bicyclic radicals with an oxygen, sulfur, or nitrogen atom are, for example, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, or benzothienyl, typically 2- or 3-benzothienyl; preferred monocyclic and bicyclic radicals with several heteroatoms are, for example, imidazolyl, typically 2- or 4-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, or thiazolyl, typically 2-thiazolyl, and benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, or quinazolyl, typically 2-quinazolinyl. Appropriate partially or, especially, completely saturated analogous radicals may also be considered, such as 2-tetrahydrofuryl, 2- or 3-pyrrolidinyl, 2-, 3-, or 4-piperidyl, and also 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl and N-mono- or N,N'-bis-lower alkyl-2-piperazinyl radicals. These radicals may also carry one or more acyclic, carbocyclic, or heterocyclic radicals, especially those mentioned hereinabove. The free valency of the heterocyclic radicals R_3 or R_4 must emanate from one of their carbon atoms. Heterocyclyl may be unsubstituted or substituted by one or more, preferably one or two, of the substituents named hereinbelow for R^o.

Heterocyclic-aliphatic radicals R_3, R_4, R_8 or R_{10} especially lower alkyl radicals, especially with a maximum of 7, preferably a maximum of 4 carbon atoms, for example those named hereinabove, which carry one, two, or more heterocyclic radicals, for example those named in the preceding paragraph, the heterocyclic ring possibly being linked to the aliphatic chain also by one of its nitrogen atoms. A preferred heterocyclic-aliphatic radical R_1 is, for example, imidazol-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, piperazin-1-ylmethyl, 2-(morpholin-4-yl)ethyl and also pyrid-3-ylmethyl. Heterocyclyl may be unsubstituted or

substituted by one or more, preferably one or two, of the substituents named hereinbelow for R°.

A heteroaliphatic radical R_3, R_4, R_8 or R_{10} with up to 20 carbon atoms each and up to 10 heteroatoms each is an aliphatic radical which, instead of one, two, or more carbon atoms, contains identical or different heteroatoms, such as especially oxygen, sulfur, and nitrogen. An especially preferred arrangement of a heteroaliphatic radical R_1 takes the form of oxa-alkyl radicals in which one or more carbon atoms are replaced in a preferably linear alkyl by oxygen atoms preferably separated from one another by several (especially 2) carbon atoms so that they form a repeating group, if need be multi-repeating group $(O\text{-}CH_2\text{-}CH_2\text{-})_q$, wherein q = 1 to 7.

Especially preferred as R_3, R_4, R_8 or R_{10}, apart from acyl, is lower alkyl, particularly methyl or ethyl; lower alkoxycarbonyl-lower alkyl, especially methoxycarbonylmethyl or 2-(tert-butoxycarbonyl)ethyl; carboxy-lower alkyl, especially carboxymethyl or 2-carboxyethyl; or cyano-lower alkyl, especially 2-cyanoethyl.

An acyl radical R_3, R_4, R_6, R_7, R_8, R_9, or $R_{10}$with up to 30 carbon atoms derives from a carboxylic acid, functionally modified if need be, an organic sulfonic acid, or a phosphoric acid, such as pyro- or orthophosphoric acid, esterified if need be.

An acyl designated Ac^1 and derived from a carboxylic acid, functionally modified if need be, is especially one of the subformula Y-C(=W)-, wherein W is oxygen, sulfur, or imino and Y is hydrogen, hydrocarbyl R° with up to 29 carbon atoms, hydrocarbyloxy R°-O-, an amino group or a substituted amino group, especially one of the formula $R^\circ HN$- or $R^\circ R^\circ N$- (wherein the R° radicals may be identical or different from one another).

The hydrocarbyl (hydrocarbon radical) R° is an acyclic (aliphatic), carbocyclic, or carbocyclic-acyclic hydrocarbon radical, with up to 29 carbon atoms each, especially up to 18, and preferably up to 12 carbon atoms, and is saturated or unsaturated, unsubstituted or substituted. Instead of one, two, or more carbon atoms, it may contain identical or different heteroatoms, such as especially oxygen, sulfur, and nitrogen in the acyclic and/or cyclic part; in the latter case, it is described as a heterocyclic radical (heterocyclyl radical) or a hetero-cyclic-acyclic radical.

Unsaturated radicals are those, which contain one or more, especially conjugated and/or isolated, multiple bonds (double or triple bonds). The term cyclic radicals includes also aromatic and non-aromatic radicals with conjugated double bonds, for example those wherein at least one 6-member carbocyclic or a 5- to 8-member heterocyclic ring contains the maximum number of non-cumulative double bonds. Carbocyclic radicals, wherein at least one ring is present as a 6-member aromatic ring (i.e. a benzene ring), are defined as aryl radicals.

An acyclic unsubstituted hydrocarbon radical R° is especially a straight-chained or branched lower alkyl-, lower alkenyl-, lower alkadienyl-, or lower alkinyl radical. Lower alkyl R° is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, and also n-pentyl, isopentyl, n-hexyl, isohexyl and n-heptyl; lower alkenyl is, for example, allyl, propenyl, isopropenyl, 2- or 3-methallyl and 2- or 3-butenyl; lower alkadienyl is, for example, 1-penta-2,4-dienyl; lower alkinyl is, for example, propargyl or 2-butinyl. In corresponding unsaturated radicals, the double bond is especially located in a position higher than the α-position in relation to the free valency.

A carbocyclic hydrocarbon radical R° is especially a mono-, bi-, or polycyclic cycloalkyl-, cycloalkenyl-, or cycloalkadienyl radical, or a corresponding aryl radical. Preference is for radicals with a maximum of 14, especially 12, ring-carbon atoms and 3- to 8-, preferably 5- to 7-, and most especially 6-member rings which can also carry one or more, for example two, acyclic radicals, for example those named above, especially the lower alkyl radicals, or other carbocyclic radicals. Carbocyclic-acyclic radicals are those in which an acyclic radical, especially one with a maximum of 7, preferably a maximum of 4 carbon atoms, such as especially methyl, ethyl and vinyl, carries one or more carbocyclic, if need be aromatic radicals of the above definition. Special mention is made of cycloalkyl-lower and aryl-lower alkyl radicals, as well as their analogues which are unsaturated in the ring and/or chain, and which carry the ring at the terminal carbon atom of the chain.

Cycloalkyl R° has most especially from 3 up to and including 10 carbon atoms and is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, as well as bicyclo[2,2,2]octyl, 2-bicyclo[2,2,1]heptyl, and adamantyl, which may also be substituted by 1, 2, or more, for example lower, alkyl radicals, especially methyl radicals; cycloalkenyl is

for example one of the monocyclic cycloalkyl radicals already named which carries a double bond in the 1-, 2-, or 3 position. Cycloalkyl-lower alkyl or -lower alkenyl is for example a -methyl, -1- or -2-ethyl, -1- or -2-vinyl, -1-, -2-, or -3-propyl or -allyl substituted by one of the above-named cycloalkyl radicals, those substituted at the end of the linear chain being preferred.

An aryl radical R^0 is most especially a phenyl, also a naphthyl, such as 1- or 2-naphthyl, a biphenylyl, such as especially 4-biphenylyl, and also an anthryl, fluorenyl and azulenyl, as well as their aromatic analogues with one or more saturated rings. Preferred aryl-lower alkyl and -lower alkenyl radicals are, for example, phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, such as for example benzyl, phenethyl, 1-, 2-, or 3-phenylpropyl, diphenylmethyl (benzhydryl), trityl, and cinnamyl, and also 1- or 2-naphthylmethyl. Aryl may be unsubstituted or substituted.

Heterocyclic radicals, including heterocyclic-acyclic radicals, are especially monocyclic, but also bi- or polycyclic, aza-, thia-, oxa-, thiaza-, oxaza-, diaza-, triaza-, or tetrazacyclic radicals of an aromatic character, as well as corresponding heterocyclic radicals of this type which are partly or most especially wholly saturated; if need be, for example as in the case of the above-mentioned carbocyclic or aryl radicals, these radicals may carry further acyclic, carbocyclic, or heterocyclic radicals and/or may be mono-, di-, or polysubstituted by functional groups. The acyclic part in heterocyclic-acyclic radicals has for example the meaning indicated for the corresponding carbocyclic-acyclic radicals. Most especially they are unsubstituted or substituted monocyclic radicals with a nitrogen, oxygen, or sulfur atom, such as 2-aziridinyl, and especially aromatic radicals of this type, such as pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3-, or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl; analogous bicyclic radicals with an oxygen, sulfur, or nitrogen atom are, for example, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, or benzothienyl, typically 2- or 3-benzothienyl; preferred monocyclic and bicyclic radicals with several heteroatoms are, for example, imidazolyl, typically 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, or thiazolyl, typically 2-thiazolyl, and benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, or quinazolyl, typically 2-quinazolinyl. Appropriate partially or, especially, completely saturated

analogous radicals may also be considered, such as 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 3-pyrrolidyl, 2-, 3-, or 4-piperidyl, and also 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl, and N,N'-bis-lower alkyl-2-piperazinyl radicals. These radicals may also carry one or more acyclic, carbocyclic, or heterocyclic radicals, especially those mentioned hereinabove. Heterocyclic-acyclic radicals are especially derived from acyclic radicals with a maximum of 7, preferably a maximum of 4 carbon atoms, for example those named hereinabove, and may carry one, two, or more heterocyclic radicals, for example those named hereinabove, the ring possibly being linked to the aliphatic chain also by one of its nitrogen atoms.

As already mentioned, a hydrocarbyl (including a heterocyclyl) may be substituted by one, two, or more identical or different substituents (functional groups); one or more of the following substituents may be considered: lower alkyl; free, etherified and esterified hydroxyl groups; carboxy groups and esterified carboxy groups; mercapto- and lower alkylthio- and, if need be, substituted phenylthio groups; halogen atoms, typically chlorine and fluorine, but also bromine and iodine; *halogen-lower alkyl groups;* oxo groups which are present in the form of formyl (i.e. aldehydo) and keto groups, also as corresponding acetals or ketals; azido groups; nitro groups; cyano groups; primary, secondary and preferably tertiary amino groups, amino-lower alkyl, mono- or disubstituted amino-lower alkyl, primary or secondary amino groups protected by conventional protecting groups (especially lower alkoxycarbonyl, typically tert-butoxycarbonyl) lower alkylenedioxy, and also free or functionally modified sulfo groups, typically sulfamoyl or sulfo groups present in free form or as salts. The hydrocarbyl radical may also carry carbamoyl, ureido, or guanidino groups, which are free or which carry one or two substituents, and cyano groups. The above use of the word "groups" is taken to imply also an individual group.

Halogen-lower alkyl contains preferably 1 to 3 halogen atoms; preferred is trifluoromethyl or chloromethyl.

An etherified hydroxyl group present in the hydrocarbyl as substituent is, for example, a lower alkoxy group, typically the methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, and tert-butoxy group, which may also be substituted, especially by (i) heterocyclyl, whereby heterocyclyl can have preferably 4 to 12 ring atoms, may be unsaturated, or partially or wholly saturated, is mono- or bicyclic, and may contain up to three heteroatoms selected

from nitrogen, oxygen, and sulfur, and is most especially pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl; and also (ii) by halogen atoms, for example mono-, di-, or polysubstituted especially in the 2-position, as in the 2,2,2-trichloroethoxy, 2-chloroethoxy, or 2-iodoethoxy radical, or (iii) by hydroxy or (iv) lower alkoxy radicals, each preferably monosubstituted, especially in the 2-position, as in the 2-methoxyethoxy radical. Such etherified hydroxyl groups are also unsubstituted or substituted phenoxy radicals and phenyl-lower alkoxy radicals, such as especially benzyloxy, benzhydryloxy, and triphenylmethoxy (trityloxy), as well as heterocyclyloxy radicals, wherein heterocyclyl can have preferably 4 to 12 ring atoms, may be unsaturated, or partially or wholly saturated, is mono- or bicyclic, and may contain up to three heteroatoms selected from nitrogen, oxygen, and sulfur, and is most especially pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2- or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl; such as especially 2- or 4-tetrahydropyranyloxy.

Etherified hydroxyl groups in this context are taken to include silylated hydroxyl groups, typically for example tri-lower alkylsilyloxy, typically trimethylsilyloxy and dimethyl-tert-butylsilyloxy, or phenyldi-lower alkylsilyloxy and lower alkyl-diphenylsilyloxy.

An esterified hydroxyl group present in the hydrocarbyl as a substituent is, for example, lower alkanoyloxy.

A carboxyl group present in the hydrocarbyl as a substituent is one in which the hydrogen atom is replaced by one of the hydrocarbyl radicals characterised hereinabove, preferably a lower alkyl- or phenyl-lower alkyl radical; an example of an esterified carboxyl group is lower alkoxycarbonyl or phenyl-lower alkoxycarbonyl substituted if need be in the phenyl part, especially the methoxy, ethoxy, tert-butoxy, and benzyloxycarbonyl group, as well as a lactonised carboxyl group.

A primary amino group $-NH_2$ as substituent of the hydrocarbyls may also be present in a form protected by a conventional protecting group. A secondary amino group carries, instead of one of the two hydrogen atoms, a hydrocarbyl radical, preferably an unsubstituted one, typically one of the above-named, especially lower alkyl, and may also be present in protected form.

A tertiary amino group present in the hydrocarbyl as substituent carries 2 different or, preferably, identical hydrocarbyl radicals (including the heterocyclic radicals), such as the unsubstituted hydrocarbyl radicals characterised hereinabove, especially lower alkyl.

A preferred amino group is one with the formula $R_{11}(R_{12})N-$, wherein R_{11} and R_{12} are independently in each case hydrogen, unsubstituted acyclic C_1-C_7-hydrocarbyl (such as especially C_1-C_4alkyl or C_2-C_4alkenyl) or monocyclic aryl, aralkyl, or aralkenyl, substituted if necessary by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen, and/or nitro, and having a maximum of 10 carbon atoms, where the carbon-containing radicals may be interlinked through a carbon-carbon bond or an oxygen atom, a sulfur atom, or a nitrogen atom substituted if necessary by hydrocarbyl. In such a case, they form a nitrogen-containing heterocyclic ring with the nitrogen atom of the amino group. The following are examples of especially preferred disubstituted amino groups: di-lower alkylamino, typically dimethylamino or diethylamino, pyrrolidino, imidazol-1-yl, piperidino, piperazino, 4-lower alkylpiperazino, morpholino, thiomorpholino and piperazino or 4-methylpiperazino, as well as diphenylamino and dibenzylamino substituted if need be, especially in the phenyl part, for example by lower-alkyl, lower-alkoxy, halogen, and/or nitro; of the protected groups, especially lower alkoxy-

carbonylamino, typically tert-butoxycarbonylamino, phenyl-lower alkoxycarbonylamino, typically 4-methoxybenzyloxycarbonylamino, and 9-fluorenylmethoxycarbonylamino.

Amino-lower alkyl is most especially substituted in the 1-position of the lower alkyl chain by amino and is especially aminomethyl.

Mono- or disubstituted amino-lower alkyl is amino-lower alkyl substituted by one or two radicals, wherein amino-lower alkyl is most especially substituted by amino in the 1-position of the lower alkyl chain and is especially aminomethyl; the amino substituents here are preferably (if 2 substituents are present in the respective amino group independently of one another) from the group comprising lower alkyl, such as especially methyl, ethyl or n-propyl, hydroxy-lower alkyl, typically 2-hydroxyethyl, C_3-C_8cycloalkyl, especially cyclohexyl, amino-lower alkyl, typically 3-aminopropyl or 4-aminobutyl, N-mono- or N,N-di(lower alkyl)-amino-lower alkyl, typically 3-(N,N-dimethylamino)propyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino.

Disubstituted amino-lower alkyl is also a 5 or 6-membered, saturated or unsaturated heterocyclyl bonded to lower alkyl via a nitrogen atom (preferably in the 1-position) and having 0 to 2, especially 0 or 1, other heteroatoms selected from oxygen, nitrogen, and sulfur, which is unsubstituted or substituted, especially by one or two radicals from the group comprising lower alkyl, typically methyl, and also oxo. Preferred here is pyrrolidino (1-pyrrolidinyl), piperidino (1-piperidinyl), piperazino (1-piperazinyl), 4-lower alkylpiperazino, typically 4-methylpiperazino, imidazolino (1-imidazolyl), morpholino (4-morpholinyl), or also thiomorpholino, S-oxo-thiomorpholino, or S,S-dioxothiomorpholino.

Lower alkylenedioxy is especially methylenedioxy.

A carbamoyl group carrying one or two substituents is especially aminocarbonyl (carbamoyl) which is substitiuted by one or two radicals at the nitrogen; the amino substituents here are preferably (if 2 substituents are present in the respective amino group independently of one another) from the group comprising lower alkyl, such as especially methyl, ethyl or n-propyl, hydroxy-lower alkyl, typically 2-hydroxyethyl, C_3-C_8cycloalkyl, especially cyclohexyl, amino-lower alkyl, typically 3-aminopropyl or 4-aminobutyl, N-mono- or N,N-di(lower alkyl)-amino-lower alkyl, typically 3-(N,N-dimethylamino)propyl, amino, N-mono- or N,N-di-lower

alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; disubstituted amino in aminocarbamoyl is also a 5 or 6-membered, saturated or unsaturated heterocyclyl with a bonding nitrogen atom and 0 to 2, especially 0 or 1, other heteroatoms selected from oxygen, nitrogen, and sulfur, which is unsubstituted or substituted, especially by one or two radicals from the group comprising lower alkyl, typically methyl, and also oxo. Preferred here is pyrrolidino (1-pyrrolidinyl), piperidino (1-piperidinyl), piperazino (1-piperazinyl), 4-lower alkylpiperazino, typically 4-methylpiperazino, imidazolino (1-imidazolyl), morpholino (4-morpholinyl), or also thiomorpholino, S-oxo-thiomorpholino, or S,S-dioxothiomorpholino.

An acyl derived from an organic sulfonic acid, which is designated Ac^2, is especially one with the subformula R^o-SO_2-, wherein R^o is a hydrocarbyl as defined above in the general and specific meanings, the latter also being generally preferred here. Especially preferred is lower alkylphenylsulfonyl, especially 4-toluenesulfonyl.

An acyl derived from a phosphoric acid, esterified if necessary, which is designated Ac^3, is especially one with the subformula $R^oO(R^oO)P(=O)$-, wherein the radicals R^o are, independently of one another, as defined in the general and specific meanings indicated above.

Reduced data on substituents given hereinbefore and hereinafter are considered to be preferences.

Preferred compounds according to the invention are, for example, those wherein R^0 has the following preferred meanings: lower alkyl, especially methyl or ethyl, amino-lower alkyl, wherein the amino group is unprotected or is protected by a conventional amino protecting group – especially by lower alkoxycarbonyl, typically tert-lower alkoxycarbonyl, for example tert-butoxycarbonyl – e.g. aminomethyl, R,S-, R- or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxycarbonylamino)ethyl, carboxy-lower alkyl, typically 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, typically 2-(tert-butoxycarbonyl)ethyl, cyano-lower alkyl, typically 2-cyanoethyl, tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)-oxymethyl, morpholino-lower alkyl, typically 2-(morpholino)ethyl, phenyl, lower alkylphenyl, typically 4-methylphenyl, lower alkoxyphenyl, typically 4-methoxyphenyl, imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl)oyxphenyl, carboxyphenyl, typically 4-carboxyphenyl, lower alkoxycarbonylphenyl,

typically 4-ethoxycarbonylphenyl or 4-methoxyphenyl, halogen-lower alkylphenyl, typically 4-chloromethylphenyl, pyrrolidinophenyl, typically 4-pyrrolidinophenyl, imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)phenyl, piperazinophenyl, typically 4-piperazinophenyl, (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl, morpholinophenyl, typically 4-morpholinophenyl, pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl, imidazol-1-yl-lower alkylphenyl, typically 4-(imidazolyl-1-ylmethyl)phenyl, piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl, (4-lower alkylpiperazinomethyl)-phenyl, typically 4-(4-methylpiperazinomethyl)phenyl, morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl, piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl, or (4-lower alkyl-piperazino)phenyl, typically 4-(4-methylpiperazino)phenyl.

Preferred acyl radicals Ac^1 are acyl radicals of a carboxylic acid which are characterised by the subformula R^o-CO-, wherein R^o has one of the above general and preferred meanings of the hydrocarbyl radical R^o. Especially preferred radicals R^o here are lower alkyl, especially methyl or ethyl, amino-lower alkyl, wherein the amino group is unprotected or protected by a conventional amino protecting group, especially by lower alkoxycarbonyl, typically tert-lower alkoxycarbonyl, for example tert-butoxycarbonyl, e.g. aminomethyl, R,S-, R-, or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxycarbonylamino)ethyl, carboxy-lower alkyl, typically 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, typically 2-(tert-butoxycarbonyl)ethyl, tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)oxymethyl, phenyl, imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl]oyxphenyl, carboxyphenyl, typically 4-carboxyphenyl, lower alkoxycarbonylphenyl, typically 4-ethoxycarbonylphenyl, halogen-lower alkylphenyl, typically 4-chloromethylphenyl, imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)phenyl, pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl, piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl, (4-lower alkylpiperazinomethyl)phenyl, typically 4-(4-methyl-piperazinomethyl)phenyl, morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl, piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl, or (4-lower alkylpiperazino)-phenyl, typically 4-(4-methylpiperazino)phenyl.

A further preferred Acyl Ac^1 is derived from monoesters of carbonic acid and is characterised by the subformula R^o-O-CO-. The lower alkyl radicals, especially tert-butyl, are especially preferred hydrocarbyl radicals R^o in these derivatives.

Another preferred Acyl Ac^1 is derived from amides of carbonic acid (or also thiocarbonic acid) and is characterised by the formula $R^oHN-C(=W)-$ or $R^oR^oN-C(=W)-$, wherein the radicals R^o are, independently of one another, as defined above and W is sulfur and especially oxygen. In particular, compounds are preferred wherein Ac^1 is a radical of formula $R^oHN-C(=W)-$, wherein W is oxygen and R^o has one of the following preferred meanings: morpholino-lower alkyl, typically 2-morpholinoethyl, phenyl, lower alkoxyphenyl, typically 4-methoxyphenyl or 4-ethoxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, or lower alkoxy-carbonylphenyl, typically 4-ethoxycarbonylphenyl.

A preferred acyl Ac^2 of subformula R^o-SO_2-, wherein R^o is a hydrocarbyl as defined in the above general and specific meanings, is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl.

If p is 0, the nitrogen atom bonding R_3 is uncharged. If p is 1, then R_4 must also be present, and the nitrogen atom bonding R_3 and R_4 (quaternary nitrogen) is then positively charged.

The definitions for an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms each, or for a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms each and up to 9 heteroatoms each, or acyl with up to 30 carbon atoms each, preferably match the definitions given for the corresponding radicals R_3 and R_4. Especially preferred is R_5 lower alkyl, especially methyl, or most especially hydrogen.

Z is especially lower alkyl, most especially methyl or hydrogen.

If the two bonds indicated by wavy lines are missing in ring A, then no double bonds (tetra-hydrogenated derivatives) are present between the carbon atoms characterised in formula I by the numbers 1, 2, 3, and 4, but only single bonds, whereas ring B is aromatic (double bonds between the carbon atoms characterised in formula I by 8 and 9 and those characterised by 10 and 11). If the two bonds indicated by wavy lines are missing in ring B, then no double bonds (tetra-hydrogenated derivatives) are present between the carbon atoms characterised in formula I by the numbers 8, 9, 10, and 11, but only single bonds, whereas ring A is aromatic (double bonds between the carbon atoms characterised in formula I by 1 and 2 and those characterised by 3 and 4). If the total of four bonds indicated by wavy lines are missing in rings A and B, and are replaced by a total of 8 hydrogen atoms,

then no double bonds (octa-hydrogenated derivatives) are present between the carbon atoms numbered 1, 2, 3, 4, 8, 9, 10, and 11 in formula I, but only single bonds.

By their nature, the compounds of the invention may also be present in the form of pharmaceutically, i.e. physiologically, acceptable salts, provided they contain salt-forming groups. For isolation and purification, pharmaceutically unacceptable salts may also be used. For therapeutic use, only pharmaceutically acceptable salts are used, and these salts are preferred.

Thus, compounds of formula I having free acid groups, for example a free sulfo, phosphoryl or carboxyl group, may exist as a salt, preferably as a physiologically acceptable salt with a salt-forming basic component. These may be primarily metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, especially tertiary monoamines and heterocyclic bases, for example triethylamine, tri-(2-hydroxyethyl)-amine, N-ethylpiperidine or N,N'-dimethylpiperazine.

Compounds of the invention having a basic character may also exist as addition salts, especially as acid addition salts with inorganic and organic acids, but also as quaternary salts. Thus, for example, compounds which have a basic group, such as an amino group, as a substituent may form acid addition salts with common acids. Suitable acids are, for example, hydrohalic acids, e.g. hydrochloric and hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid or perchloric acid, or aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, fumaric, maleic, hydroxymaleic, oxalic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, anthranilic, p-hydroxybenzoic, salicylic, p-aminosalicylic acid, pamoic acid, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenedisulfonic, halobenzenesulfonic, toluenesulfonic, naphthalenesulfonic acids or sulfanilic acid, and also methionine, tryptophan, lysine or arginine, as well as ascorbic acid.

In view of the close relationship between the compounds (especially of formula I) in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, and of their solvates, any reference hereinbefore and hereinafter to the free compounds is to be understood as

referring also to the corresponding salts, and the solvates thereof, for example hydrates, as appropriate and expedient.

The compounds of formula A, B, C, D, I, II, III, IV, V or VI especially those wherein R_5 is hydrogen, possess valuable pharmacological properties.

In the case of the groups of radicals or compounds mentioned hereinbefore and hereinafter, general definitions may, insofar as appropriate and expedient, be replaced by the more specific definitions stated hereinbefore and hereinafter.

Preference is given to a compounds of formula I, II, III, IV, V, VI wherein
R_1 and R_2 independently of each other are lower alkyl, lower alkyl substituted by halogen, C_6-C_{14}aryl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkyl-carbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower - alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl; halogen; lower alkoxy; C_6-C_{14}aryloxy; C_6-C_{14}aryl-lower alkoxy; lower alkanoyloxy; C_6-C_{14}arylcarbonyloxy; amino monosubstituted or disubstituted by lower alkyl, C_6-C_{14}aryl, C_6-C_{14}aryl-lower alkyl, lower alkanoyl or C_6-C_{12}aryl-carbonyl; cyano; nitro; mercapto; lower alkylthio; C_6-C_{14}arylthio; C_6-C_{14}aryl-lower alkylthio; lower alkanoylthio; C_6-C_{14}aryl-lower alkanoylthio; carboxy; lower alkoxycarbonyl, C_6-C_{14}aryl-lower alkoxycarbonyl; C_6-C_{14}aryloxycarbonyl; carbamoyl; carbamoyl N-mono- or N,N-disubstituted by lower alkyl, C_6-C_{14}aryl or C_6-C_{14}aryl-lower alkyl; sulfo; C_6-C_{14}arylsulfonyl; C_6-C_{14}aryl-lower alkanesulfonyl; lower alkanesulfonyl; or aminosulfonyl N-mono- or N,N-disubstituted by lower alkyl, C_6-C_{14}aryl or C_6-C_{14}aryl-lower alkyl, wherein C_6-C_{14}aryl is an aryl radical with 6 to 12 carbon atoms in the ring system, which may be unsubstituted or substituted by halogen, phenyl or naphthyl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkylcarbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl;

n and m are independently of each other 0 or 1 or 2, preferably 0;

R_3, R_4, R_8, R_{10} are independently of each other hydrogen, lower alkyl, lower alkenyl or lower alkadienyl, which are each unsubstituted or monosubstituted or polysubsituted, preferably monosubstituted or disubstituted by a substituent independently selected from lower alkyl; hydroxy; lower alkoxy, which may be unsubstituted or mono-, di-, or trisubstituted by (i) heterocyclyl with 4 to 12 ring atoms, which may be unsaturated, wholly saturated, or partly saturated, is monocyclic or bicyclic and may contain up to three heteroatoms selected from nitrogen, oxygen and sulfur, and is most especially pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, or in a broader sense also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, (ii) by halogen, (iii) by hydroxy or (iv) by lower alkoxy; phenoxy; phenyl-lower alkoxy; heterocyclyloxy, wherein heterocyclyl is pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, or in a broader sense also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, such as especially 2- or 4-tetrahydropyranyloxy; lower alkanoyloxy; carboxy; lower alkoxycarbonyl; phenyl-lower alkoxycarbonyl; mercapto; lower alkylthio; phenylthio; halogen; halogen-lower alkyl; oxo (except in the 1-position, because otherwise acyl); azido; nitro; cyano; amino; mono-lower alkylamino; di-lower alkylamino; pyrrolidino; imidazol-1-yl; piperidino; piperazino; 4-lower

alkylpiperazino; morpholino; thiomorpholino; diphenylamino or dibenzylamino unsubstituted or substituted in the phenyl part by lower alkyl, lower alkoxy, halogen and/or nitro; lower alkoxycarbonylamino; phenyl-lower alkoxycarbonylamino unsubstituted or substituted in the phenyl part by lower alkyl or lower alkoxy; fluorenylmethoxycarbonylamino; amino-lower alkyl; monosubstituted or disubstituted amino-lower alkyl, wherein the amino substituent is selected from lower alkyl, hydroxy-lower alkyl, C_3-C_8cycloalkyl, amino-lower alkyl, N-mono- or N,N-di(-lower alkyl)amino-lower alkyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; pyrrolidino-lower alkyl; piperidino-lower alkyl; piperazino-lower alkyl; 4-lower alkylpiperazino-lower alkyl; imidazol-1-yl-lower alkyl; morpholino-lower alkyl; thiomorpholino-lower alkyl; S-oxo-thiomorpholino-lower alkyl; S,S-dioxothiomorpholino-lower alkyl; lower alkylendioxy; sulfamoyl; sulfo; carbamoyl; ureido; guanidino; cyano; aminocarbonyl (carbamoyl) and aminocarbonyloxy, which are substituted by one or two radicals on the nitrogen, wherein the amino substituents are selected independently of one another from the group comprising lower alkyl, hydroxy-lower alkyl, C_3-C_8cycloalkyl, amino-lower alkyl, N-mono- or N,N-di(-lower alkyl)amino-lower alkyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; pyrrolidinocarbonyl; piperidinocarbonyl; piperazinocarbonyl; 4-lower alkylpiperazinocarbonyl; imidazolinocarbonyl; morpholinocarbonyl; thiomorpholinocarbonyl; S-oxo-thio-morpholinocarbonyl; and S,S-dioxothiomorpholino;

phenyl, naphthyl, phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, which is unsubstituted or monosubstituted or disubstituted by the radicals named above as substituents of lower alkyl, lower alkenyl or lower alkadienyl;

or heterocyclyl-lower alkyl, wherein heterocyclyl is pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, or in a broader sense also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-

piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, which in each case are unsubstituted or monosubstituted or disubstituted by the radicals named above as substituents of lower alkyl, lower alkenyl, or lower alkadienyl;

or acyl of the subformula Y-C(=W)-, wherein W is oxygen and Y is hydrogen, R^o, R^o-O-, R^oHN-, or R^oR^oN- (wherein the radicals R^o may be the same or different),
or
acyl of the subformula R^o-SO_2-,
whereby R_4 may also be absent for the compound of formula II;

or
R_4 is absent for compounds of formula II, hydrogen or CH_3 for compounds of formula I, and R_3 is acyl of the subformula Y-C(=W)-, wherein W is oxygen and Y is hydrogen, R^o, R^o-O-, R^oHN-, or R^oR^oN- (wherein the radicals R^o may be the same or different),
or
is acyl of the subformula R^o-SO_2-,

wherein R^0 in the said radicals has the following meanings: substituted or unsubstituted lower alkyl, especially methyl or ethyl, amino-lower alkyl hydroxy-lower alkyl, wherein the amino group is unprotected or is protected by a conventional amino protecting group – especially by lower alkoxycarbonyl, typically tert-lower alkoxycarbonyl, for example tert-butoxycarbonyl – e.g. aminomethyl, R,S-, R- or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxycarbonylamino)ethyl, carboxy-lower alkyl, typically 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, typically 2-(tert-butoxycarbonyl)ethyl, cyano-lower alkyl, typically 2-cyanoethyl, tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)oxymethyl, morpholino-lower alkyl, typically 2-(morpholino)ethyl, phenyl, lower alkylphenyl, typically 4-methylphenyl, lower alkoxyphenyl, typically 4-methoxyphenyl, imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl)oxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, lower alkoxycarbonylphenyl, typically 4-ethoxycarbonylphenyl or 4-methoxyphenyl, halogen-lower alkylphenyl, typically 4-chloromethylphenyl, pyrrolidinophenyl, typically 4-pyrrolidinophenyl, imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)phenyl, piperazinophenyl, typically 4-piperazinophenyl, (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl, morpholinophenyl, typically 4-morpholinophenyl, pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl,

imidazol-1-yl-lower alkylphenyl, typically 4-(imidazolyl-1-ylmethyl)phenyl, piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl, (4-lower alkylpiperazinomethyl)-phenyl, typically 4-(4-methylpiperazinomethyl)phenyl, morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl, piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl, or (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl.

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals (for compounds of formula II);

R_5 is hydrogen or lower alkyl, especially hydrogen,

X stands for 2 hydrogen atoms, for O, or for 1 hydrogen atom and hydroxy; or for 1 hydrogen atom and lower alkoxy;

Z is hydrogen or especially lower alkyl, most especially methyl;

and for compounds for formula II, either the two bonds characterised by wavy lines are preferably absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or also the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

Particular preference is given to a compound of formula I wherein;
m and n are each 0;
R_3 and R_4 are independently of each other
hydrogen,

lower alkyl unsubstituted or mono- or disubstituted, especially monosubstituted, by radicals selected independently of one another from carboxy; lower alkoxycarbonyl; and cyano;;
or
R_4 is hydrogen or $-CH_3$, and
R_3 is as defined above or preferably R_3 is,
acyl of the subformula R^o-CO, wherein R^o is lower alkyl; amino-lower alkyl, wherein the amino group is present in unprotected form or is protected by lower alkoxycarbonyl; tetrahydropyranyloxy-lower alkyl; phenyl; imidazolyl-lower alkoxyphenyl; carboxyphenyl; lower alkoxycarbonylphenyl; halogen-lower alkylphenyl; imidazol-1-ylphenyl; pyrrolidino-lower alkylphenyl; piperazino-lower alkylphenyl; (4-lower alkylpiperazinomethyl)phenyl; morpholino-lower alkylphenyl; piperazinocarbonylphenyl; or (4-lower alkylpiperazino)phenyl;

or is acyl of the subformula R^o-O-CO-, wherein R^o is lower alkyl;

or is acyl of the subformula R^oHN-C(=W)-, wherein W is oxygen and R^o has the following meanings: morpholino-lower alkyl, phenyl, lower alkoxyphenyl, carboxyphenyl, or lower alkoxycarbonylphenyl;

or R_3 is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl;

further specific examples of preferred R_3 groups are described below for the preferred compounds of formula II,

R_5 is hydrogen or lower alkyl, especially hydrogen,
X stands for 2 hydrogen atoms or for O;
Z is methyl or hydrogen;

or a salt thereof, if at least one salt-forming group is present.

Particular preference is given to a compound of formula II wherein
m and n are each 0;
R_3 and R_4 are independently of each other
hydrogen,

lower alkyl unsubstituted or mono- or disubstituted, especially monosubstituted, by radicals selected independently of one another from carboxy; lower alkoxycarbonyl; and cyano; whereby R_4 may also be absent;
or
R_4 is absent, and
R_3 is acyl from the subformula R°-CO, wherein R° is lower alkyl, especially methyl or ethyl; amino-lower alkyl, wherein the amino group is unprotected or protected by lower alkoxy-carbonyl, typically tert-lower alkoxycarbonyl, for example tert-butoxycarbonyl, e.g. aminomethyl, R,S-, R-, or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxycarbonylamino)ethyl; tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)oxymethyl; phenyl; imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl)oyxphenyl; carboxyphenyl, typically 4-carboxyphenyl; lower alkoxycarbonylphenyl, typically 4-methoxy- or 4-ethoxycarbonylphenyl; halogen-lower alkylphenyl, typically 4-chloromethylphenyl; imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)-phenyl; pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl; piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl; (4-lower alkylpiperazinomethyl)phenyl, typically 4-(4-methylpiperazinomethyl)phenyl; morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl; piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl; or (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl;

or is acyl of the subformula R°-O-CO-, wherein R° is lower alkyl;

or is acyl of the subformula R°HN-C(=W)-, wherein W is oxygen and R° has the following preferred meanings: morpholino-lower alkyl, typically 2-morpholinoethyl, phenyl, lower alkoxyphenyl, typically 4-methoxyphenyl or 4-ethoxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, or lower alkoxycarbonylphenyl, typically 4-ethoxycarbonylphenyl;

or is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl;

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;
R_5 is hydrogen or lower alkyl, especially hydrogen,
X stands for 2 hydrogen atoms or for O;
Z is methyl or hydrogen;

and either the two bonds characterised by wavy lines are preferably absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or also the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

Most especially preferred compounds of formula II are selected from;
8,9,10,11-Tetrahydrostaurosporine;
N-[4-(4-methylpiperaziN-1-ylmethyl)benzoyl]-1,2,3,4-tetrahydrostaurosporine;
N-(4-chloromethylbenzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-(pyrrolidin-1-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-(morpholin-4-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-(piperazin-1-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-ethyl-1,2,3,4-tetrahydrostaurosporine;
N-tosyl-1,2,3,4-tetrahydrostaurosporine;
N-triflouroacetyl-1,2,3,4-tetrahydrostaurosporine;
N-[4-(2-imidazol-1-yl-ethoxy)benzoyl]-1,2,3,4-tetrahydrostaurosporine;
N-methoxycarbonylmethyl-1,2,3,4-tetrahydrostaurosporine;
N-carboxymethyl-1,2,3,4-tetrahydrostaurosporine;
N-terephthaloylmethyl ester-1,2,3,4-tetrahydrostaurosporine;
N-terephthaloyl-1,2,3,4-tetrahydrostaurosporine;
N-(4-ethylpiperazinylcarbonylbenzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(2-cyanoethyl)-1,2,3,4-tetrahydrostaurosporine;
N-benzoyl-1,2,3,4-tetrahydrostaurosporine;
N,N-dimethyl -1,2,3,4-tetrahydrostaurosporinium iodide;
N-BOC-glycyl-1,2,3,4-tetrahydrostaurosporine;

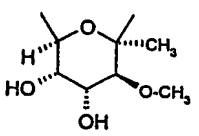
N-glycyl-1,2,3,4-tetrahydrostaurosporine;
N-(3-(tert-butoxycarbonyl)propyl)-1,2,3,4-tetrahydrostaurosporine;
N-(3-carboxypropyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-imidazol-1-yl)benzoyl]-1,2,3,4-tetrahydrostaurosporine;
N-[(tetrahydro-2h-pyran-4-yloxy)acetyl]-1,2,3,4-tetrahydrostaurosporine;
N-BOC-l-alanyl-1,2,3,4-tetrahydrostaurosporine;
N-l-alanyl-1,2,3,4-tetrahydrostaurosporine hydrochloride;
N-methyl-1,2,3,4-tetrahydro-6-methylstaurosporine;
N-(4-carboxyphenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-ethylphenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
N-(N-phenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
N-(N-[2-(1-morpholino)ethyl]aminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
N-(N-[4-methoxyphenyl]aminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
1,2,3,4-tetrahydro-6-methylstaurosporine;
N-BOC-1,2,3,4-tetrahydrostaurosporine;
N-BOC-1,2,3,4-tetrahydro-6-methylstaurosporine;
N-BOC-1,2,3,4-tetrahydro-6-methyl-7-oxo-staurosporine;
1,2,3,4,8,9,10,11-octahydrostaurosporine;
or a pharmaceutically acceptable salt thereof, if at least one salt-forming group is present.

Most especially preferred is the compound of formula I designated 1,2,3,4-tetrahydro-staurosporine, or a (particularly pharmaceutically acceptable) salt thereof (here, m und n in formula I are 0, R_3 is hydrogen, R_4 is absent, provided no salt is present (p = 0), or is hydrogen if a salt is present (p = 1), R_5 is hydrogen, the two bonds represented by wavy lines are absent in Ring A and are replaced by a total of 4 hydrogen atoms and the two bonds represented by wavy lines in Ring B are in each case a double bond together with the parallel bonds, X stands for 2 hydrogen atoms, and Z is methyl).

Most especially preferred are the compounds of formula A wherein;

A) X= O; R_1, R_2, R_5 = H; Q= $-(CH_2)_2-O-CH(CH_2)OH-(CH_2)_2-$

B) X= O; R_1, R_2, R_5 = H; Q= $-(CH_2)_2-O-CH(CH_2N(CH_3)_2)-(CH_2)_2-$

C) X= 2 hydrogen atoms; R_1, R_2, R_5 = H; Q= 

Most especially preferred are the compounds of formula I wherein;

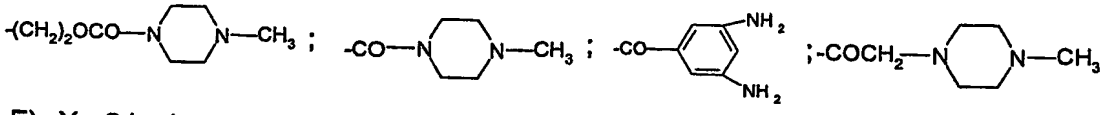
A) X= 2 hydrogen atoms; R_1,R_2, R_3, R_5 = H; R_4= CH_3; Z=CH_3 (staurosporine)

B) X= 1 hydrogen and 1 hydroxy atoms in (R) or (S) isomeric form; R_1,R_2, R_3,R_5 = H; R_4= CH_3; Z=CH_3 (UCN-01 and UCN-02)

C) X= 2 hydrogen atoms; R_1,R_2, R_5 = H; R_4= CH_3; R_3,= benzoyl; Z=CH_3 (CGP41251 or PKC412 or MIDOSTAURIN)

D) X= O; R_1,R_2, R_5 = H; R_3,= CH_3; R_4= ethyloxycarbonyl; Z=CH_3 (NA 382 ; CAS=143086-33-3)

E) X= 1 hydrogen and 1 hydroxy atom; R_1, R_2, R_5 = H; R_3= CH_3; Z=CH_3; and R_4 is selected from $-(CH_2)_2OH$; $-CH_2CH(OH)CH_2OH$; $-CO(CH_2)_2CO_2Na$; $-(CH_2)_3CO_2H$; $-COCH_2N(CH_3)_2$;



F) X= 2 hydrogen atoms; R_1, R_2, R_5 = H; R_3= CH_3; Z=CH_3; and R_4 is selected from N-[0-(tetrahydropyran-4-yl)-D-lactoyl]; N-[2-methyl-2-(tetrahydropyran-4-yloxy)-propionyl; N-[0-(tetrahydropyran-4-yl)-L-lactoyl]; N-[0-(tetrahydropyran-4-yl)-D-lactoyl]; N-[2-(tetrahydro-pyran-4-yloxy)-acetyl)]

G) X=O; R_1, R_2, R_5 = H; R_3= CH_3; Z=CH_3; and R_4 is selected from N-[0-(tetrahydropyran-4-yl)-D-lactoyl]; N-[2-(tetrahydro-pyran-4-yloxy)-acetyl)]

H) X=1 hydrogen and 1 hydroxy atom ; R_1, R_2, R_5 = H; R_3= CH_3; Z=CH_3; and R_4 is selected from N-[0-(tetrahydropyran-4-yl)-D-lactoyl]; N-[2-(tetrahydro-pyran-4-yloxy)-acetyl)]

The abbreviation "CAS" means the CHEMICAL ABSTRACTS registry number.

The most preferred compounds of formula I e.g. MIDOSTAURIN [International Nonproprietary Name] are covered and have been specifically described by the European patent No. 0 296 110 published on December 21, 1988, as well as in US patent No. 5;093,330 published on March 3, 1992, and Japanese Patent No. 2 708 047. Other preferred compounds are covered and described by the patent applications WO 95/32974 and WO 95/32976 both published on December 7, 1995. All the compounds described in these documents are incorporated into the present application by reference.

Most especially preferred are the compounds of formula III wherein;

A) X= 2 hydrogen atoms; R_1,R_2, R_5 = H; R_6= CH_3; R_7= methyloxycarbonyl; Z=H (2-methyl K252a)

B) X= 2 hydrogen atoms; R_1,R_2, R_5, R_6 = H; R_7= methyloxycarbonyl; Z= H (K-252a)

C) X= 2 hydrogen atoms; R_1,R_2, R_5, R_6 = H; R_7= methyloxycarbonyl; Z= CH_3 (KT-5720)

Most especially preferred are the compounds of formula IV wherein;

A) X= O; R_1, R_2, R_5 = H; R_9= CH_2-NMe_2; R_8= CH_3 ; m'=n'=2

B) X= O; R_1, R_2, R_5 = H; R_9= CH_2-NH_2; R_8= CH_3 ; m'=2; n'=1 (Ro-31-8425; CAS=151342-35-7)

Most especially preferred are the compounds of formula V wherein;

A) X= O; R_1, R_2, R_5 = H; R_8= CH_3; R_{10}= -$(CH_2)_3$-NH_2; (Ro-31-7549; CAS=138516-31)

B) X= O; R_1, R_2, R_5 = H; R_8= CH_3; R_{10}= -$(CH_2)_3$-S-(C=NH)-NH_2; (Ro-31-8220 ; CAS=125314-64-9))

C) X= O; R_1, R_2, R_5 = H; R_8= CH_3; R_{10}= -CH_3;

Most especially preferred are the compounds of formula VI wherein;

A) X= 2 hydrogen atoms; R_1,R_2, R_5 = H; R_4= CH_3; Z=CH_3 ; R_3 selected from methyl or (C_1-C_{10})alkyl, arylmethyl, $C_6H_2CH_2$-

STAUROSPORINE DERIVATIVES and their manufacturing process have been specifically described in many prior art documents, well known by the man skilled in the art.

Compounds of formula A, B, C, D and their manufacturing process have for instance, been described in the European patents No. 0 657 458 published on June 14, 1995, in the European patents No. 0 624 586 published on November 17, 1994, in the European patents No. 0 470 490 published on February 12, 1992, in the European patents No. 0 328 026 published on August 16, 1989, in the European patents No. 0 384 349 published on August 29, 1990, as well as in many publications such as *Barry M. Trost* and Weiping Tang* Org. Lett., 3(21), 3409-3411.

Compounds of formula I and their manufacturing processes have specifically been described in the European patents No. 0 296 110 published on December 21, 1988, as well as in US patent No. 5;093,330 published on March 3, 1992, and Japanese Patent No. 2 708 047. Compounds of formula I having a tetrahydropyran-4-yl)-lactoyl substitution on R_4 have been described in the European patent No. 0 624 590 published on November 17, 1994. Other compounds have been described in the European patent No. 0 575 955 published December 29, 1993, European patent No. 0 238 011 published on September 23, 1987

(UCN-01), International patent application EP98/04141 published as WO99/02532 on July 03, 1998.

Compounds of formula II and their manufacturing processes have specifically been described in the European patents No. 0 296 110 published on December 21, 1988, as well as in US patent No. 5;093,330 published on March 3, 1992, and Japanese Patent No. 2 708 047.

Compounds of formula III and their manufacturing processes have specifically been described in the patent applications claiming the priority of the US patent application US 920102 filed on July 24, 1992. (i.e European patents No. 0 768 312 published on April 16, 1997, No. 1 002 534 published May 24, 2000, No. 0 651 754 published on May 10, 1995).

Compounds of formula IV and their manufacturing processes have specifically been described in the patent applications claiming the priority of the British patent applications GB 9309602 and GB 9403249 respectively filed on May 10, 1993, and on February 21, 1994. (i.e European patents No. 0 624 586 published on November 17, 1994, No. 1 002 534 published May 24, 2000, No. 0 651 754 published on May 10, 1995).

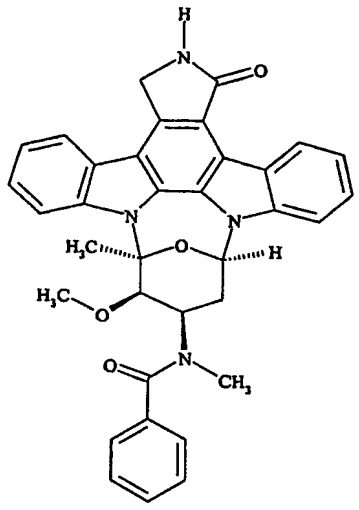
Compounds of formula V and their manufacturing processes have specifically been described in the patent applications claiming the priority of the British patent applications GB 8803048, GB 8827565, GB 8904161 and GB 8928210 respectively filed on February 10, 1988, November 25, 1988, February 23, 1989 and December 13, 1989. (i.e European patents No. 0 328 026 published on August 16, 1989, and No. 0 384 349 published August 29, 1990).

Compounds of formula VI and their manufacturing processes have specifically been described in the patent applications claiming the priority of the US patent applications 07/777,395 (Con), filed on October 10, 1991 (i.e International patent application WO 93/07153 published on April 15, 1993).

In each case where citations of patent applications or scientific publications are given in particular for the STAUROSPORINE DERIVATIVE compounds, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

The preferred STAUROSPORINE DERIVATIVE according to the invention is *N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the formula (VII):



(VII)

or a salt thereof, (hereinafter: "Compound of formula VII or MIDOSTAURIN").

Compound of formula VII is also known as MIDOSTAURIN [International Nonproprietary Name] or PKC412.

MIDOSTAURIN is a derivative of the naturally occurring alkaloid staurosporine, and has been specifically described in the European patent No. 0 296 110 published on December 21, 1988, as well as in US patent No. 5;093,330 published on March 3, 1992, and Japanese Patent No. 2 708 047.

It has now surprisingly been found that MIDOSTAURIN possesses therapeutic properties, which render it particularly useful as an inhibitor of PDGFRα (platelet derived growth factor α, also abbreviated as PDGRA) and especially for the treatment of FIP1L1-PDGFRα-induced diseases like hypereosinophilic syndrome. FIP1L1-PDGFRα, as used hereinbefore and

hereinafter, is the designation of the fusion product of the genes FIP1L1 (FIP1 like 1) with PDGFRα. Particularly surprising is that Midostaurin is effective in the prevention or treatment of imatinib-induced resistance, which is believed to occur because of the T674I mutation in FIP1L1-PDGFRα.

STAUROSPORINE DERIVATIVES e.g. MIDOSTAURIN were originally identified as inhibitor of protein kinase C (PKC) (Meyer T, Regenass U, Fabbro D, et al: Int J Cancer 43: 851-856, 1989).

It has now surprisingly been found that STAUROSPORINE DERIVATIVES possess therapeutic properties, which render them particularly useful as an inhibitor of FIP1L1-PDGFRα and especially in the treatment and prophylaxis of hypereosinophilic syndrome and hypereosinophilic syndrome with resistance to imatinib. In particular MIDOSTAURIN shows an unexpected high potency toward the FIP1L1-PDGFRαT674I mutation.

The present invention thus concerns the use of STAUROSPORINE DERIVATIVES for the preparation of a drug for the treatment of FIP1L1-PDGFRα-induced myeloproliferative diseases, or other diseases associated with FIPL1-PDGFRa or similar mutations that activate PDGFRα..

The term "FIP1L1-PDGFRα-induced myeloproliferative diseases" as used herein includes, but is not limited to, hypereosinophilic syndrome and hypereosinophilic syndrome with resistance to imatinib. This term also specifically includes diseases resulting from FIP1L1-PDGFRα mutation, particularly from the FIP1L1-PDGFRαT674I mutation.

The present invention more particularly concerns the use of STAUROSPORINE DERIVATIVES for the preparation of a drug for the treatment of hypereosinophilic syndrome and hypereosinophilic syndrome with resistance to imatinib.

In another embodiment, the instant invention provides a method for treating FIP1L1-PDGFRα-induced myeloproliferative diseases comprising administering to a mammal in need of such treatment a therapeutically effective amount of STAUROSPORINE DERIVATIVES, or pharmaceutically acceptable salts or prodrugs thereof.

Preferably the instant invention provides a method for treating mammals, especially humans, suffering from FIP1L1-PDGFRα-induced myeloproliferative diseases comprising

administering to a mammal in need of such treatment a FIP1L1-PDGFRα inhibiting amount of *N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the formula (VII), or a pharmaceutically acceptable salt thereof.

The instant invention also concerns a method wherein the therapeutically effective amount of the compound of formula VII is administered to a mammal subject 7 to 4 times a week or about 100 % to about 50% of the days in the time period, for a period of from one to six weeks, followed by a period of one to three weeks, wherein the agent is not administered and this cycle being repeated for from 1 to several cycles.

Preferably, this method is used for treating FIP1L1-PDGFRα-induced myeloproliferative diseases .

More preferably, this method is used for treating hypereosinophilic syndrome or hypereosinophilic syndrome with resistance to imatinib.

In another embodiment, the instant invention relates to the use of STAUROSPORINE DERIVATIVES for the preparation of a pharmaceutical composition for use in treating FIP1L1-PDGFRα-induced myeloproliferative diseases, more particularly for treating hypereosinophilic syndrome or hypereosinophilic syndrome with resistance to imatinib.

STAUROSPORINE DERIVATIVES have useful pharmacological properties. In particular, MIDOSTAURIN inhibits the growth of FIP1L1-PDGFRα expressing Ba/F3 cells in concentrations in the range of 130 nM.

In vivo, the activity of the STAUROSPORINE DERIVATIVES especially compounds of formula I or II, can be demonstrated, for example, in a single or up to three oral administrations per day to animals at doses in the range of 0.1 to 10 or 1 to 5 mg/kg of body weight per day.

The STAUROSPORINE DERIVATIVES are therefore very highly suitable for the treatment of diseases, which are FIP1L1-PDGFRα-induced myeloproliferative diseases, e.g. hypereosinophilic syndrome or hypereosinophilic syndrome with resistance to imatinib.

FIP1L1-PDGFRα is a cause of hypereosinophilic syndrome and a therapeutic target for the tyrosine kinase inhibitor imatinib (International Non-proprietary Name), which is marketed under the designation GLEEVEC ® in the US and GLIVEC ® in Europe.

It was surprisingly found that when a relapse occurs during the treatment of hypereosinophilic syndrome with imatinib very often a T674I mutation in PDGFRα is diagnosed.

This has prompted the applicant to search for new inhibitors of the FIP1L1-PDGFRα activity as a possible therapeutic approach in these patients, for whom current drug therapies offer little utility, and for such patients who have previously failed current available drug therapies and/or stem cell transplantation therapies.

In the present description, the term "treatment" includes both prophylactic or preventative treatment as well as curative or disease suppressive treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease as well as ill patients. This term further includes the treatment for the delay of progression of the disease.

The term "curative" as used herein means efficacy in treating ongoing episodes involving FIP1L1-PDGFRα-induced myeloproliferative diseases.

The term "prophylactic" means the prevention of the onset or recurrence of diseases involving FIP1L1-PDGFRα-induced myeloproliferative diseases.

The term "delay of progression" as used herein means administration of the active compound to patients being in a pre-stage or in an early phase of the disease to be treated, in which patients for example a pre-form of the corresponding disease is diagnosed or which patients are in a condition, e.g. during a medical treatment or a condition resulting from an accident, under which it is likely that a corresponding disease will develop.

This unforeseeable range of properties means that the use of STAUROSPORINE DERIVATIVES are of particular interest for the manufacture of a medicament for the treatment of diseases involving FIP1L1-PDGFRα-induced myeloproliferative diseases. In particular MIDOSTAURIN has a high safety margin, high affinity and selectivity.

This effect can especially be clinically relevant for patients with hypereosinophilic syndrome or hypereosinophilic syndrome with resistance to imatinib.

To demonstrate that STAUROSPORINE DERIVATIVES are particularly suitable for the treatment of FIP1L1-PDGFRα-induced myeloproliferative diseases with good therapeutic margin and other advantages, clinical trials can be carried out in a manner known to the skilled person.

The precise dosage of STAUROSPORINE DERIVATIVES to be employed for inhibiting inhibiting FIP1L1-PDGFRα activity or for treating FIP1L1-PDGFRα-induced myeloproliferative diseases depends upon several factors including the host, the nature and the severity of the condition being treated, the mode of administration. However, in general, satisfactory inhibition of FIP1L-PDGFRα is achieved when the STAUROSPORINE DERIVATIVE is administered parenterally, e.g., intraperitoneally, intravenously, intramuscularly, subcutaneously, intratumorally, or rectally, or enterally, e.g., orally, preferably intravenously or, preferably orally, intravenously at a daily dosage of 0.1 to 10 mg/kg body weight, preferably 1 to 5 mg/kg body weight. In human trials a total dose of 225 mg/day was most presumably the Maximum Tolerated Dose (MTD). A preferred intravenous daily dosage is 0.1to 10 mg/kg body weight or, for most larger primates, a daily dosage of 200-300 mg. A typical intravenous dosage is 3 to 5 mg/kg, three to five times a week.

Most preferably, the STAUROSPORINE DERIVATIVES, especially MIDOSTAURIN, are administered orally, by dosage forms such as microemulsions, soft gels or solid dispersions in dosages up to about 250 mg/day, administered once, twice or three times daily.

Usually, a small dose is administered initially and the dosage is gradually increased until the optimal dosage for the host under treatment is determined. The upper limit of dosage is that imposed by side effects and can be determined by trial for the host being treated.

The STAUROSPORINE DERIVATIVES may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, e.g. orally, in the form of tablets, capsules, caplets, etc. or parenterally, e.g., intraperitoneally or intravenously, in the form of

sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

The infusion solutions according to the present invention are preferably sterile. This may be readily accomplished, e.g. by filtration through sterile filtration membranes. Aseptic formation of any composition in liquid form, the aseptic filling of vials and/or combining a pharmaceutical composition of the present invention with a suitable diluent under aseptic conditions are well known to the skilled addressee.

The STAUROSPORINE DERIVATIVES may be formulated into enteral and parenteral pharmaceutical compositions containing an amount of the active substance that is effective for inhibiting FIP1L1-PDGFRα, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

The STAUROSPORINE DERIVATIVES can be used alone or combined with at least one other pharmaceutically active compound for use in these pathologies. These active compounds can be combined in the same pharmaceutical preparation or in the form of combined preparations "kit of parts" in the sense that the combination partners can be dosed independently or by use of different fixed combinations with distinguished amounts of the combination partners, i.e., simultaneously or at different time points. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Non-limiting examples of compounds which can be cited for use in combination with STAUROSPORINE DERIVATIVES are cytotoxic chemotherapy drugs, such as cytosine arabinoside, daunorubicin, doxorubicin, cyclophosphamide, VP-16, or imatinib etc. Further, STAUROSPORINE DERIVATIVES could be combined with other inhibitors of signal transduction or other oncogene-targeted drugs with the expectation that significant synergy would result.

Examples of useful compositions are described in the European patents No. 0 296 110, No. 0 657 164, No. 0 296 110, No.0 733 372, No.0 711 556, No.0 711 557.

The preferred compositions are described in the European patent No. 0 657 164 published on June 14, 1995. The described pharmaceutical compositions comprise a solution or

dispersion of compounds of formula I such as MIDOSTAURIN in a saturated polyalkylene glycol glyceride, in which the glycol glyceride is a mixture of glyceryl and polyethylene glycol esters of one or more C8-C18 saturated fatty acids.

Two manufacture processes of such compositions are described hereafter.

Composition A:

Gelucire 44/14 (82 parts) is melted by heating to 60° C. Powdered MIDOSTAURIN (18 parts) is added to the molten material. The resulting mixture is homogenised and the dispersion obtained is introduced into hard gelatin capsules of different size, so that some contain a 25mg dosage and others a 75mg dosage of the MIDOSTAURIN. The resulting capsules are suitable for oral administration.

Composition B:

Gelucire 44/14 (86 parts) is melted by heating to 60° C. Powdered MIDOSTAURIN (14 parts) is added to the molten material. The mixture is homogenised and the dispersion obtained is introduced into hard gelatin capsules of different size, so that some contain a 25mg dosage and others a 75mg dosage of the MIDOSTAURIN. The resulting capsules are suitable for oral administration.

Gelucire 44/14 available commercially from Gattefossé; is a mixture of esters of C8-C18 saturated fatty acids with glycerol and a polyethylene glycol having a molecular weight of about 1500, the specifications for the composition of the fatty acid component being, by weight, 4-10% caprylic acid, 3-9% capric acid, 40-50% lauric acid, 14-24% myristic acid, 4-14% palmitic acid and 5-15% stearic acid.

A preferred example of Gelucire formulation consists of:
Gelucire (44/14): 47 g
MIDOSTAURIN: 3.0g filled into a 60 mL Twist off flask

A preferred example of soft gel will contain the following Microemulsion:

Cornoil glycerides	85.0 mg
Polyethylenglykol 400	128.25 mg
Cremophor RH 40	213.75 mg

MIDOSTAURIN	25.0 mg
DL alpha Tocopherol	0.5 mg
Ethanol absolute	33.9 mg
Total	486.4 mg

However, it should be clearly understood that it is for purposes of illustration only.

In a preferred embodiment this invention relates to use or method as described herein, wherein the daily effective amount of the compound of formula VII, is 100 to 300 mg, preferably 125 mg to 250 mg most preferably 220 to 230 mg, preferably 225 mg.

Most preferably the compound of formula VII, is administered once, twice or three times a day, for a total dose of 100 to 300 mg daily.

In a very preferred embodiment the compound of formula VII, is administered three times a day, for a total dose of 220 to 230 preferably 225 mg daily, and preferably at a dose per administration of 70 to 80 mg, preferably 75 mg.

In still another embodiment, this invention relates to an article of manufacture comprising packaging material, and *N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the formula (VII) or a pharmaceutically acceptable salts thereof, contained within said packaging material, wherein said packaging material comprises label directions which indicate that said compound of formula (VII), or said pharmaceutically-acceptable salt, is to be administered to mammals suffering from FIP1L1-PDGFRα-induced myeloproliferative diseases, in an amount from 50 to 500 mg, preferably 100 to 300 mg, preferably 125 mg to 250 mg, more preferably 220 to 230 mg, most preferably 225 mg following a specific dosage regimen to inhibit the development of FIP1L1-PDGFRα induced myeloproliferative diseases.

Preferably to an article of manufacture wherein the compound of formula VII, is administered three times a day, for a total dose of 220 to 230mg, preferably 225 mg daily, and preferably a dose of 70 to 80 mg, most preferably 75 mg, per administration for the treatment of hypereosinophilic syndrome or hypereosinophilic syndrome with resistance to imatinib. A

preferred embodiment relates to an article of manufacture comprising softgel capsules containing 25 mg of the compound of formula VII.

The invention further pertains the combination of a STAUROSPORINE DERIVATIVE as described hereinbefore with imatinib for the treatment of the diseases and conditions described hereinbefore. The administration of such a combination may be affected at the same time, for instance in the form of a fixed, combined pharmaceutical composition or preparation, or sequentially or timely staggered. The administration of a STAUROSPORINE DERIVATIVE in a dosage form as described hereinbefore and of imatinib in its marketed form of GLEEVEC ® in the US/GLIVEC® in Europe and with the dosages envisaged for these dosage forms is currently preferred.

The treatment of FIP1L1-PDGFRα-induced myeloproliferative diseases with the above combination may be a so-called first line treatment, i.e. the treatment of a freshly diagnosed disease without any preceeding chemotherapy or the like, or it may also be a so-called second line treatment, i.e. the treatment of the disease after a preceeding treatment with imatrinib or a STAUROSPORINE DERIVATIVE, depending on the severity or stage of the disease as well as the over all condition of the patient etc..

The efficacy of STAUROSPORINE DERIVATIVES for the treatment of FIP1L1-PDGFRα-induced myeloproliferative diseases is illustrated by the results of the following examples. These examples illustrate the invention without in any way limiting its scope:

The retroviral construct MSCV-FIP1L1-PDGFRα-ires-EGFP and the corresponding T674I mutant were described previously (Cools et al., New England Journal of Medicine Vol. 348 No. 13, p 1201-1214 2003). The N659D mutation was introduced by PCR (polymerase chain reaction).

Cell culture and retroviral transduction

293T cells were grown in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10 % FBS (fetal bovine serum). Ba/F3 cells were grown in RPMI (Rosweli Park Memorial Institute) medium supplemented with 10 % FBS and 1 ng/ml mouse IL-3. Production of retroviral vectors and transduction was described. Transformed Ba/F3 cells were grown in the absence of IL3. The kinase inhibitors imatinib and PKC412 were stored as 10 mM stock

solutions in water (imatinib) or DMSO (dimethylsulfoxide) (PKC412). These inhibitors were diluted in RPMI medium for use. For western blotting, Ba/F3 cells were incubated in the presence of imatinib for 90 minutes before lysis. For dose response curves, Ba/F3 cells were incubated for 24 hours in the presence of imatinib and the number of viable cells at the start and end point was determined by use of the Celltiter96AQ$_{ueous}$one solution proliferation assay (Promega). Dose response curves were fitted using the OriginPro 6.1 software (OriginLab, Northampton, MA).

Bone marrow transplantation and treatment of the animals

Balb/c mice were purchased from Taconic (Germantown, NY). Bone marrow transplant assays (injecting 1 x 10^6 cells per recipient mouse) and drug treatment of the mice was performed as described previously (Schwaller et al., 1998; Kelly et al.; Weisberg et al., 2002). Imatinib (stored as powder at 4 °C) was resuspended in a 0.5 % methylcellulose (MC) solution in water prior to use. PKC412 (6% w/w in Gelucire® 44/14 (GC) (Gattefosse,France)) was stored at 4 °C as a waxy-solid formulation. Prior to administration, the GC/PKC412 waxy solid mixture was melted in a 44 °C water bath and diluted with sterilized deionized water. The animals were weighed at regular basis to ensure that a consistent dose (150 mg/kg/day for imatinib and 100 mg/kg/day for PKC412) of drug was administered. Dosing was performed every 12 hr for imatinib and every 24 hr for PKC412 by oral gavage of a maximum volume of 150 µl per animal using 22 gauge gavage needles (Hornbecks). Placebo animals received the same volume of a MC or GC solution. Any animals with splenomegaly (spleen boundary detectable at the dorsal medline) or that were moribund were sacrificed and analysed for signs of hematological disease.
Peripheral blood was collected from the retroorbital cavity using a heparinized glass capillary. Blood smears were stained with Wright and Giemsa. Manual and automated (ADIVA 120 Hematology system, Bayer) total and differential blood cell counts were performed. Histopathologic exam of relevant organs (spleen, liver, heart, lungs, intestine, hindlimb bones, and kidneys) and preparation of single-cell suspensions from spleen and bone marrow for flow cytometry was performed as described. In comparing the survival time of the mice, all times are measured from the day of BMT (bone marrow transplant), and the log rank test is used to attach a significance level to the difference in the survival curve.

Histopathology

Murine tissues were fixed for at least 72 hours in 10 % neutral buffered formalin (Sigma), dehydrated in alcohol, cleared in xylene, and infiltrated with paraffin on an automated processor (Leica, Bannockburn, IL). The tissue sections (4 µm) from paraffin-embedded tissue blocks were placed on charged slides and deparaffinized in xylene, rehydrated through graded alcohol solutions, and stained with hematoxylin and eosin.

Immunoprecipitation and Western blotting

Immunoprecipitation was performed using the anti-Myc antibody (Cell Signaling) and Protein G agarose (Roche). Each precipitation was started from $6x10^6$ Ba/F3 cells stably expressing myc-tagged FIP1L1-PDGFRα wild type or T674I mutant. Cells were lysed in lysis buffer (Cell Signaling) containing 1 mM Na_3VO_4, 20 µM phenylarsine oxide (Calbiochem) and complete tablets (Roche). For western blotting, Ba/F3 cells were collected by centrifugation and directly lysed in 1 x loading buffer containing 2 % SDS (sodium dodecyl sulfate) and 40 µM DTT (dithiothreitol) (Cell Signaling), separated using 10 - 12 % SDS-PAGE (SDS-Poly Acrylamide Gel Electrophoresis) and transferred to membranes. The antibodies used were: anti-phospho-STAT5 and anti-phospho-tyrosine (P-Tyr-100/102) (Cell Signaling), anti-PDGFRα (Upstate), anti-STAT5b (Santa-Cruz), anti-mouse-PO and anti-rabbit-PO (Amersham Pharmacia Biotech). Detection was performed using the Western Lightning system (Perkin Elmer).

The following tables illustrate the efficacy of MIDOSTAURIN (PKC412) in the treatment of FIP1L1-PDGFRα-induced myeloproliferative diseases by way of example only:

Table 1. Efficacy of imatinib for the treatment of FIP1L1-PDGFRα-induced myeloproliferative disease, and resistance to FIP1L1-PDGFRα(T674I)-induced disease (trial 1).

	FIP1L1-PDGFRα wild type		FIP1L1-PDGFRαT674I
	placebo	imatinib	imatinib
spleen weight (g)			
mean	832	111	801

median	852	106	780
range	667 - 922	93 - 140	700 - 1,007
n	8	8	6
WBC (x 10^6/ml)			
mean	654.4	6.0	496.5
median	620.2	5.2	507.7
range	593.8 - 773.0	4.6 - 9.4	434.6 - 535.8
n	5	7	4

Spleen weights and white blood cell counts (WBC) of mice in the different groups of trial 1, determined on time of death or at trial endpoint. n: number of mice analysed.

Table 2. Efficacy of PKC412 (MIDOSTAURIN) for the treatment of both FIP1L1-PDGFRα- and FIP1L1-PDGFRα(T674I)-induced myeloproliferative disease (trial 2).

	FIP1L1-PDGFRα		
	placebo	**imatinib**	**PKC412**
spleen weight (g)			
mean	729	101	241
median	690	99	199
range	588 - 922	82 - 132	104 - 586
n	9	9	8
WBC (x 10^6/ml)			
mean	534.1	4.8	12.7
median	554.3	4.8	12.4
range	388.9 - 639.0	4.4 - 5.3	5.8 - 20.0
n	4	4	3

	FIP1L1-PDGFRα T674I		
	placebo	**imatinib**	**PKC412**
spleen weight (g)			
mean	743	649	157
median	778	645	157
range	556 - 803	543 - 785	90 - 217
n	7	8	9
WBC (x 10^6/ml)			
mean	493.2	548.2	3.8
median	460.6	591.5	3.1
range	28.7 - 879.8	364.9 - 657.6	1.9 - 7.2
n	5	7	6

Spleen weights and white blood cell counts (WBC) of mice in the different groups of trial 2, determined on time of death or at trial endpoint. n: number of mice analysed.